REMARKS

Claims 1, 3, 5 and 14 are pending in the application. Claims 6 and 7 are hereby cancelled. Claims 2, 4 and 8 to 13 have been previously cancelled. Claim 14 is new and is supported by original claims 1, 3 and 5. No new matter has been introduced by way of the present response.

According to the response of July 11, 2007 to the last restriction requirement, Applicant had elected "gout" as the specific disease, and "intravenous administration" as the specific route of administration, both of which are readable on the pending claims. Examiner, upon further consideration, has extended the examination to include "subcutaneous" administration.

Claim 1 now recites:

> *"A method for inhibiting the recruitment of neutrophils causative of an inflammatory reaction in a human individual, said method comprising administering to said individual an antibody against extracellular S100A8 protein and an antibody against extracellular S100A9 protein, thereby inhibiting the recruitment of said neutrophils of said individual."*

It is submitted by Applicant that the invention covers the administration of antibodies which are directed towards S100A8 and S100A9 proteins which, when found extracellularly in inflammatory lesions of a patient represent the cause of an inflammatory reaction *thereby inducing migration of neutrophils that contribute to the inflammatory process (i.e. chemotaxis).* In contrast, the binding of such antibodies to intracellular S100A8 and S100A9 proteins would not contribute to reducing the inflammatory symptoms since intracellular S100A8 and S100A9 do not contribute to neutrophils migration but are rather involved in other intracellular pathways, such as for example, degranulation of neutrophils.

As is shown in the accompanying Declaration, degranulation of neutrophils does not provoke secretion of S100A8 and S100A9. Therefore, injection of antibodies against S100A8 and S100A9 would not represent a treatment for inflammation when S100A8 and S100A9 are present only intracellularly and exert their intracellular effect.

Title

The title of the invention has been found as allegedly not being descriptive by the Examiner. The Applicant has amended the title to read:

> *"ANTIBODIES AGAINST S100A8 AND S100A9 PROTEINS FOR MODULATING INFLAMMATORY REACTIONS".*

Specification

Pages 4, 8 and 18 have been amended to correct grammatical errors (page 4, first paragraph and page 8, last paragraph) and to add a missing trademark identification (page 18, second paragraph).

Claim rejections – 35 USC § 102

Claims 1 and 5 to 7 have been rejected by the Examiner as allegedly being anticipated by Hanash as evidenced by Seto et al. Reconsideration of this rejection is respectfully requested based on the following arguments.

In paragraphs [0110-0112], Hanash teaches production of antibodies, techniques well known in the art, whereas paragraph [0116] simply indicates that the antibody portion is useful for locating and *targeting the cells* which contain the S100 proteins:

> *"[0016] The antibodies produced may be conjugated with a radioactive tag and injected into a patient. With appropriate imaging techniques the tumor can be located (emphasis added) using the radioactively conjugated antibody. If the amount of radioactivity attached to the antibody is increased considerably, or the antibody is conjugated to a toxin or an anti-tumor drug, the conjugate can be used to kill tumor cells in vivo. The antibody provides the targeting function, (emphasis added) and the toxin, anti-tumor drug or radioactivity kills the cells which are targeted by the antibody. The radioactive tag can be any isotope giving off alpha particles, beta particles or gamma rays. The toxin can be any substance, such as ricin, known to be toxic to cells. The anti-tumor drug includes any drug, e.g. daunorubicin, 5-fluorouracil, or derivatives thereof, or methotrexate,*

effective in treating tumors. Using an antibody conjugated with radioactivity, a toxin or drug for tumor therapy is known in the art, for instance see Roitt, I. et al, Immunology, pp. 20.8 and 20.9, Mosby, London, 1996, which is incorporated by reference. An effective dose can be 0.0005 to 500 mg antibody per kg body weight. The conjugate can be administered by intravenous, intramuscular or subcutaneous injections."

In paragraph [0125], Hanash teaches that the presence of S100A8 and A9 near lung tumors indicates that infiltrative cells, either neutrophils, monocytes and/or macrophages, were being found at the tumor site, nothing more. Hanash mentions that both neutrophils and monocytes express high levels of S100A8/A9 in their cytosol, representing up to 30% of neutrophil cytosolic proteins:

"[0125] An antibody against the cystic fibrosis antigen (an epitope formed by heterodimerization of MRP8 and PRP14) also will react positively against a 14kDa antigen which has been shown to be MRP14. The antibody is available commercially. This antibody has been utilized for immunohistochemistry on sections of tumor tissue (emphasis added) and corresponding normal tissue from the same patient. These stained tissue sections revealed minimal staining in the normal lung tissue. There was somewhat more reactivity in the tumor tissue, most probably due to the increased presence of infiltrative cells. Of note, however, there was a very large amount of immunoreactivity in the area of normal tissue immediately adjacent to the tumor, thus suggesting that infiltrative cells (i.e., granulocytes, monocytes and/or macrophages) were being recruited to the tumor (emphasis added). Moreover, whether the antibody would recognize a specific 14 kDa protein in the serum of lung tumor patients was explored, at levels greater than that which might be present in the serum of normal individuals. The serum of 14 lung tumor patients and 14 normal individuals was separated by 1D electrophoresis, the proteins were transferred to PVDF membranes and probed with the commercial antibody. Integrated intensity analysis of reactivity in the serum from tumor patients (n=14; mean intensity of 0.46) as compared to that in the serum from normal individuals (n=14; mean intensity of 0.09)."

In paragraph [0126], Hanash discloses the presence of MRP-8 (e.g. S100A8) and MRP-14 (e.g. S100A9) near lung tumors, and describes the use of these proteins in the screening for different types of cancer:

> *"[0126] These findings indicate a role for antibodies against MRP in screening for different types of cancer in which the MRP's are detected in tumor tissue."*

Hanash does not teach that neutrophils at the tumor site secrete extracellular S100A8 and S100A9. Hanash does not teach that secreted, extracellular S100A8 and S100A9 have migratory activity for recruiting more neutrophils. By reading the reference of Hanash, the skilled person in the art would have concluded that the detection of S100A8 and A9 is a confirmation of the presence of cells expressing these proteins intracellularly. By reading the reference of Hanash, the skilled person in the art would NOT have concluded that the detection of S100A8 and A9 is a cause of the migration of these cells near the tumor.

Seto teaches that S100A8 and S100A9 can also be designated as MRP-8 and MRP-14 respectively.

By reading the reference by Hanash as evidenced by Seto, the skilled man in the art would therefore have understood the combined teachings of these two references as a method for confirming the presence of intracellular S100A8 and A9 proteins in secretory cells at tumor sites and confirming the intracellular role of S100A8 and A9 in cell degranulation.

Therefore, it is submitted that neither of these references disclose, suggest or leads one skilled in the art to envision a method for inhibiting the recruitment of neutrophils involved in inflammatory reactions according to the present patent application, neutrophil recruitment being an extracellular process.

Claim rejections – 35 USC § 103

Claims 1, 3 and 5 to 7 have been rejected as allegedly being obvious over Seto *et al.* in view of Hanash and Dinerstein et al. Reconsideration of this rejection is respectfully requested based on the following arguments.

Seto teaches the intracellular injection of antibodies to block the intracellular activity of S100A8 and A9, which, according to Seto, are important for neutrophil degranulation. As stated by the Examiner in the office action:

> "*The reference teach that **secretion** (emphasis added) of granules by neutrophils can be inhibited by administering polyclonal antibodies to calgranulin, which comprise calgranulin A (aka S100A8) and calgranulin B (aka AS100A9) into cell lines*".

Secretion of granules occurs via degranulation. Since degranulation is an intracellular process, the skilled person in the art would NOT have considered an intracellular protein (S100A8 and A9) involved in an intracellular pathway (degranulation) as having a pro-inflammatory *extracellular* activity. In fact, very few intracellular proteins have extracellular activities. Most of them, for example, MAP kinases, PI3 kinases and tubulin are involved in neutrophil degranulation, but do not exert any extracellular effect. **In contrast, and as proposed for the first time by the Applicant, the present patent application addresses an extracellular mechanism of S100A8 and A9 i.e. cell migration upon secretion, which is a process different from degranulation** (see attached declaration of Philippe Tessier).

An important point to understand is that S100A8 and S100A9 are NOT secreted upon neutrophil degranulation. S100A8 and A9 only act intracellularly to *induce* degranulation of other secretory proteins contained in macrophages granules upon activation. Therefore, the skilled person in the art would have found no motivation in trying to inhibit an extracellular mechanism such as neutrophil recruitment by blocking intracellular proteins such as S100A8 and S100A9 from exerting their respective intracellular effects on cell degranulation.

Once again, Hanash discloses a method for confirming the presence of intracellular S100A8 and A9 proteins in secretory cells at tumor sites and confirming the intracellular role of S100A8 and A9 in cell degranulation.

Dinerstein discloses the implication of neutrophils in gout. However, even by combining this reference with the ones of Hanash and Seto, the skilled man in the art would have found no indication on how to inhibit the recruitment of neutrophils by blocking extracellular S100A8 and A9 proteins. As stated previously, the skilled person in the art would very well understand that the references by Hanash and by Seto address the implication of S100A8 and A9 in neutrophil degranulation, and would have certainly known that degranulation is an intracellular process that does not involve extracellular activity of S100A8 and A9 on neutrophil recruitment.

In support of these arguments, the Applicant is submitting the enclosed declaration of Philippe Tessier along with a reference by Ryckman et al. (Journal of Leucocytes Biology 76, page 433-440, 2004) demonstrating that the secretion of S100A8/A9 by neutrophils is performed by a mechanism different than the one involved in the action of S100A8 and A9 on cell degranulation.

Conclusion

In conclusion, it was known that:

- in the cells, S100A8 and S100A9 play a role in neutrophil degranulation;
- *but* S100A8 and S100A9 are *not* secreted upon neutrophil degranulation;
- S100A8 and S100A9 are secreted under other circumstances which have no relationship with degranulation.

It was unknown that:

- when secreted (i.e. extracellular), S100A8 and S100A9 play a *causative* role in inflammation by recruiting neutrophils through chemotaxis.

With respect, the Examiner has failed to establish a *prima facie* case of obviousness since she cited prior art that disclose *only* the involvement of intracellular S100A8 and S100A9 in neutrophil degranulation. None of the prior art cited disclose or point to the involvement of extracellular S100A8 and S100A9 in neutrophil recruitement causing inflammation.

The Examiner is therefore respectfully requested to withdraw the rejections.

It is therefore submitted that the claims are in condition for allowance. Examination on the merits is respectfully requested and allowance of claims 1, 3, 5 and 14 at an early date is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

A two-month extension fee of 230$ for small entity status is believed to be required in the filing of the present Response to Office Action. No other fees are believed to be required by the present response. However, should this be an error, authorization is hereby given to charge deposit account 19-5113 for any underpayment or to credit any overpayment.

Respectfully submitted,

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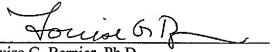

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encl. Declaration of Philippe Tessier along with c.v.
IDS and 4 references